BUILDING QUALITY INTO CLINICAL TRIALS – AN FDA PERSPECTIVE

Jean Toth-Allen, Ph.D.
Biophysicist
Office of Good Clinical Practice
Office of the Commissioner

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Overview

- I. Background – why we are talking about "building in quality"
- II. Elements of a quality system – and how they are related to FDA regulations
- III. Building in quality from the start – and improving on-going studies
- IV. Clinical Trial Transformation Initiative (CTTI)

I. Background -1

- Increasing concerns regarding the safety of medical products
- Reports that the general public is losing confidence in clinical trials
- Increasing complexity of medical products and studies
- Multisite, international studies
- Increasing cost of traditional monitoring
- Recognition that we cannot monitor or inspect in quality

Background –2

FDA's bioresearch monitoring (BIMO) program

- Program objectives
  - Protect the rights, safety, and welfare of subjects in FDA-regulated trials
  - Determine the accuracy and reliability of clinical trial data submitted to FDA in support of research or marketing applications; and
  - Assess compliance with FDA's regulations governing the conduct of clinical trials, including those for informed consent and ethical review

Background -3

- FDA's BIMO Program (cont.)
  - Covers all regulated products
  - Number of studies actually inspected limited by available resources
  - Generally inspects after studies completed, though shifting more resources to "real-time" inspections
  - Inspects selected study sites – may not be able to extrapolate findings to overall study

Background –4

- Quality systems approach – first developed for manufacturing; embraced by other endeavors (ISO 9001 = international standard)
- Shared responsibility for quality, but the quality systems approach emphasizes “management” (sponsor) responsibility

What Is Quality?*

"Quality" is characterized by the ability to

- Effectively and efficiently answer the intended question about the benefits and risks of a medical product (therapeutic or diagnostic) or procedure

while

- Ensuring protection of human subjects

* Definition from October 2008 presentation on CTTI by Dr. Rachel Behrman, CTTI Co-chair and then Associate Commissioner for Clinical Programs, FDA (presently director of CDER's Office of Medical Policy)

II. Elements of a quality clinical study

- Scientifically valid and ethically sound experimental design
- Adequate protection of subjects rights, safety, and welfare
- Qualified personnel
- “Adequate” monitoring
- Current, complete, and accurate data

FDA regulations -1

- Scientifically valid and ethical
  - FDA review for significant risk studies
  - IRB review for all FDA-regulated studies
- Subject protection
  - Informed consent process requirements (21 CFR Part 50; required elements of informed consent document at 50.25)
- Qualified personnel
  - Sponsor required to choose investigators and monitors with appropriate training and experience (21 CFR 312.53, 511.1(b)(7)(i), 511.1(b)(8)(ii), & 812.43)

FDA regulations -2

- "Adequate" monitoring – little further information in regulations (21 CFR 312.56 and 812.46)
  - Assure investigator compliance – with investigational plan and regulations
  - Review adverse events and determine impact on continuation of the study
- Current, complete, and accurate data – investigators required to collect and maintain; sponsors monitor compliance

III. Suggestions for a quality study – the regulations and beyond

- Select qualified investigators
- *Assure protocol & data requirements optimized*
- Provide adequate training
  - *Stress importance of informed consent process*
- Ensure adequate monitoring
- Ensure investigator compliance
- *Ensure any and all contracted 3rd parties comply with the appropriate regulations*

Select qualified investigators -1

- More than a CV review and consideration of status in the medical/veterinary community
- Need to determine if the clinical investigator and his/her site have:
  - Adequate time, staff, equipment, & ancillary support systems
  - Knowledge of applicable regulations & guidance
  - Commitment to research

Select qualified investigators -2

- Investigator/staff have (cont.):
  - Understanding that the Form FDA 1572 and Investigator agreement = contract to be compliant
  - Awareness of the difference between a clinician and a clinical investigator
  - Recognition of the implications of the “therapeutic misconception”
  - Appropriate skills and experience with similar products – dependent upon the nature of the product; more relevant for device studies

Select qualified investigators -3

- Certification – for clinical investigators and other study staff – available from various professional associations
- FDA regulations do not require but many industry sponsors consider it a positive when seeking study sites
- Provides additional assurance of familiarity with essentials

Optimizing the protocol

- Appropriate investigator input prior to finalization
- Inclusion/exclusion criteria appropriate and not unnecessarily restrictive
- Timing of procedures clinically appropriate
- “Testing,” initially and at follow-up visits, appropriate to the study endpoints

INTERACTIONS UP FRONT CAN AVOID COSTLY PROTOCOL DEVIATIONS

Optimization success story -1

- Two pediatric oncology studies
- Study staff from all sites brought together for brain-storming session on draft protocols
- Major issue – 6 large pills required twice a day
- A participant knew of a “sippy cup” design = Oralflo to aid with swallowing pills

Optimization success story -2

- Studies planned for 1 year and 2 years, respectively
- Actually completed in 6 months and 1 year
- No protocol amendments required
- Minimal protocol deviations
- No substantive findings from FDA BIMO inspections

Optimizing the dataset

- Errors happen! – minimize impact by collecting only essential data
  - relevant and critical to safety and effectiveness endpoints
  - meet all guidance recommendations, where applicable
  - captured via checklists, limited to numbers, and/or to a few descriptive words
  - “less can be more” – avoid duplicate copies
  - dialogue with FDA review division where appropriate

Protocol deviations -1

On-going study

- Monitoring reports evidence continued deviations
- Analyze to determine if:
  - site specific or common across study
  - specific initial or follow-up testing commonly omitted
  - specific group of inappropriate subjects included
  - common set of data elements missing or inaccurate
  - subject non-compliance high

Protocol deviations -2

If problems across sites:

- Discussion with investigators might suggest reason (s)
- Study salvageable or new study needed?
- Might require discussion with FDA review division
- New enrollment on hold until decision made?
- Expanded population or different endpoint or test may be needed

Training

Before study & when essential staff replaced

- Specific study expectations
- Procedures unique to the product or the study
- Regulatory requirements
- Human factors concerns (essential for many device studies; relevant to the expanding use of e-documents)
- Importance of the informed consent process

Informed consent process

- Well-informed participants:
  - Understand study requirements
  - Are less likely to drop out due to unexpected procedures
  - Are more likely to be compliant with essential details
- Appropriate updates can allay fears, stave off inaccurate rumors, reinforce commitment

"Retraining"/updates

On-going study

- Significant changes to product or protocol
- Monitoring reveals problems
  - Follow-up guidance and queries do not appear to bring compliance
  - Significant subject noncompliance – renewed emphasis on informed consent process
  - Compelling reasons to retain site

Monitoring – 1

- Limited FDA guidance available
  - January 1988 – Guideline for the Monitoring of Clinical Investigations – removed from FDA website - spoke to "traditional monitoring"
  - Draft guidance – issued August 2011 – describes a risk-based approach to monitoring, including the use of central monitoring http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf

Monitoring – 2

- Limited FDA guidance available
  - ICH E6 (GCP guidance) – 1997 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf
  - Veterinary ICH (VICH GL9), 2001 http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052417.pdf

Monitoring -3

Study monitoring

- Only one aspect of sponsor oversight of a clinical trial
- Standard Operating Procedures (SOPs) for all aspects of study conduct essential
- CDER's Office of Medical Policy (OMP) spearheading finalization of draft monitoring guidance
- One of the approved projects under CTTI

Traditional monitoring -1

- Early & frequently enough for the specific study
- Rationale
  - Early – ensures understanding
  - Frequently – catches problems and noncompliance before repeated
  - Systemic issues can be corrected before study integrity is jeopardized
  - Regular source document verification avoids numerous queries and late database problems
  - Training opportunities for new and/or non-compliant study staff or amended protocol

Traditional monitoring -2

- Follows well-developed SOPs, which can be modified to meet changing study needs
- Critical areas typically reviewed at visits include:
  - Human subject protection (HSP) areas (informed consent and IRB)
  - Compliance with investigational plan and regulations
  - Protocol deviations – reasons examined
  - Source document verification
  - Case report forms (CRFs) current, complete, and accurate
  - Product accountability current, complete, and accurate

Monitoring – new considerations

- FDA recognizes traditional monitoring may not be cost-effective for the large, multinational trials common today
- Draft document on risk-based monitoring clarifies that various approaches to monitoring are possible
- Risk-based approach needed for efficiency and effectiveness
- Single “process” not always the best
- Combinations of methods, e.g., central and on-site monitoring, suggested

Central monitoring

- Includes
  - remote data checks for
    - **missing or invalid data**
    - **calendar discrepancies**
    - **unusual data patterns**
  - assessment of rates of data reporting, including adverse events
  - assessment of predetermined performance indicators
  - comparisons with external sources

Site monitoring

- On-site visits, the mainstay of traditional monitoring, probably cannot be completely ruled out for any monitoring model
- Central monitoring, statistical risk determinations, and/or other methods may provide guides as to the frequency and emphasis of visits
- Site visits essential for:
  - Training on protocol, procedures, and pertinent regulations
  - Verification of site resources
  - Verification of compliance with protocol and regulations

Compliance

- Predetermined strategy for obtaining
- Expeditious sponsor review of monitoring reports
- Immediate actions to correct noncompliance
- Where applicable, product shipments halted until evidence of compliance
- If all else fails, site's participation in study terminated
- Report to FDA review division

3rd party compliance -1

- Transfer of regulatory responsibility to a contract research association (CRO) possible under 21 CFR 312.52 and 511.1(b)(4)(vi)
- Does not relieve sponsor of responsibility
- Concerns about study can result in FDA refusal to accept results in support of marketing
- Device regulations do not address CROs, therefore device study sponsors are directly responsible for everything contracted to 3rd parties

3rd party compliance -2

- Other “entities” supporting clinical studies (Site Management Organizations (SMOs), data handling/processing companies)
- Not covered by current FDA regulations
- Sponsor audits before contracting and during study are strongly recommended – to review SOPs for adequacy and actual work accomplished

IV. Clinical Trial Transformation Initiative (CTTI)* -1

- A public private partnership (PPP)
- Established out of a shared vision
  - Current problem (clinical trials enterprise is being strangled and, therefore, cannot answer the pressing questions facing society)
  - Path forward (focus on the enterprise as a ***quality system***, e.g., 'product' must be fit for use) *(emphasis added)*
  - Mutual need (no one entity can fix this alone and certainly not in a timely manner)

* CTTI slides courtesy of an October 2008 presentation by Dr. Rachel Behrman

CTTI -2

- MOU between Duke and FDA announced in FR 11/2007
  - Duke and FDA share an interest in HSP and modernizing the clinical trials enterprise
  - Duke convened a PPP, with FDA and Duke as founding partners, that includes a broad coalition of stakeholders, e.g., regulated industry (pharmaceutical, device, and biotechnology companies and CROs), academia, professional societies, trade organizations, clinical investigator groups, patient advocacy groups, government agencies (funding and regulatory)

CTTI Mission/Scope

- To identify practices that through broad adoption will increase the ***quality**** and efficiency of clinical trials

*emphasis added

Once again – What Is Quality?

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CTTI Scope, *cont*.

- Generate evidence about how to improve the *design* and *execution* of clinical trials
- Projects about design will address principles generally applicable to clinical trials to ensure that they will accomplish their intended purpose

CTTI Scope, *cont.*

- May study other types of clinical research (e.g., registries) that can provide data to regulatory agencies
- May seek to identify practice improvements that can be applied internationally

CTTI Principles

- In seeking to protect and promote the public health by generating adequate and timely information about prevention, diagnosis, and treatment of disease, the clinical trial enterprise must hold paramount the need to protect human subjects, including their privacy.

- All interested entities must work together to move the system forward; we encourage the input and participation of all stakeholders. No single constituency will have a controlling influence.

CTTI Projects

- Information about the process for submission, review, and approval of projects available at CTTI Web site: https://www.trialstransformation.org/projects

- Priority areas defined by Executive Committee:
  - Design principles
  - Data quality and quantity (including monitoring)
  - Study start-up
  - Adverse event reporting

CTTI Projects

- Quality by Design (QbD) a major current interest
- First workshop held August 2011
- Plan to expand those participating – beyond drug studies and beyond sponsors

Continuing resources -1

- GCP website- http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm

- Alias – http://www.fda.gov/gcp

- Also available from FDA site index under “good clinical practice”

Continuing resources -2

- GCP queries e-mail account (about 1,200 queries answered per year) – gcp.questions@fda.hhs.gov
- Previous queries (2002 – 2010) – “Replies to queries…” link from GCP website (bottom of left-hand column)
- Listserve – via GCP website – notice of updates on FDA’s GCP/HSP activities

Continuing resources -3

BIMO contacts available at:

http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm134476.htm